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Disease-a-Month

Rheumatoid Arthritis

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RHEUMATOID ARTHRITIS is a syndrome of unknown etiology and obscure pathogenesis with symptoms primarily referable to joint structures and skeletal musculature. It is characterized by a nonspecific inflammatory reaction appearing commonly in these tissues but occasionally in other sites in the body (1). Peripheral joint rheumatoid arthritis is seen also in two variant forms: rheumatoid arthritis associated with psoriasis, and the juvenile disease. The characteristics of each, as well as of another possible variant—Marie-Strümpell spondylitis, will be discussed.

Many causative agents have been implicated and each has been discarded because of insufficient evidence. Logic alone, not experimental data, suggests that the characteristic of a

sustained inflammatory reaction is best explained on the basis of hypersensitivity with an element of autosensitization to a tissue component. There is evidence, not generally accepted, that the initial lesion is an arteritis (35) with subsequent development of a granulomatous—chronic inflammatory—change (see further, on p. 11). Statistics in this disease are misleading, and in this discussion, percentages regarding incidence or prevalence of certain findings will be avoided. The literature contains widely varying percentages for the descriptive aspects of almost any phase of the disease. Certain features are correlated with severe disease, and if the group studied includes a large number of patients with severe disease, the incidence of the finding will be high. The same thinking applies to all aspects of the disease, including natural history, evaluation of agents for treatment and prognosis. These will be less favorable in a group made up largely of patients with severe disease; more favorable when consisting of patients with mild disease.

DIAGNOSIS

A major difficulty is the problem of diagnosis. Patients with typical sustained disease constitute only a relatively small percentage of patients seen at a given point in time, respond less favorably to accepted measures of treatment and give no insight into the prognosis of early disease. Frequently, early symptoms and signs are episodic without persistent and irreversible changes. During an episode, the diagnosis may appear obvious, but during remission a retrospective diagnosis may be obscure. A simple, reliable diagnostic test is not available, and study of the natural history of the disease is suspect since diagnosis is often based upon personal opinion. Efforts are in progress attempting, by fiat if not by knowledge, to lay down diagnostic criteria. If an investigator applies these criteria to his patients, a better appraisal of treatment claims will be possible, but these efforts will not solve the problems of prognosis in early disease. There is no prognostic test.

Many syndromes may be confused with rheumatoid arthritis in its early phases. Recently, even the patient with chronic advanced rheumatoid arthritis has been observed to develop systemic lupus erythematosus (SLE). Whether this was lupus throughout the disease or lupus superimposed on rheumatoid arthritis cannot yet be determined. However, SLE may appear, apparently more frequently, in patients with chronic rheuma-

toid arthritis than in the general population. A positive Hargraves preparation and manifestations of renal, central nervous system, serosal, myocardial, or hemopoietic involvement with thrombocytopenia or hemolytic anemia all would make one consider SLE before rheumatoid arthritis. With the early disease, an elevated erythrocyte sedimentation rate may help distinguish rheumatoid arthritis from degenerative joint disease and fibrositis where manifestations of inflammation are lacking. With gout, a prompt response to colchicine is the only definitive diagnostic tool. With rheumatic fever, the presence of carditis, a complete response of the arthritis to salicylates, a pre-existing upper respiratory infection, or an elevated antistreptolysin titer may all be invoked to exclude rheumatoid arthritis.

Laboratory tests used as diagnostic aids may be classified as those which probably represent the host response and those which may represent the disease. The difference is arbitrary, based upon the effect on the patient of large amounts of an anti-inflammatory agent such as cortisone when host response is decreased. In these circumstances, certain serologic reactions remain consistently positive, and we believe that these may represent the disease itself rather than a manifestation of host response. The reactions include the agglutination of group A hemolytic streptococci (2) and the various procedures using agglutination of sensitized sheep cells. The former is a difficult technical procedure which cannot be applied routinely. The sheep cell agglutination reaction is undergoing extensive investigation and its technique is in a state of transition. In the near future a modification of this test may be available which is sensitive, relatively simple, and of help in early or atypical disease (3–6).

Other serologic diagnostic aids represent nonspecific host responses to inflammation—elevated erythrocyte sedimentation rate, hypoalbuminemia, hyperglobulinemia—with a nondescript elevation of α and γ globulin, C-reactive protein, cephalin flocculation, etc.

The principal diagnostic aid in rheumatoid arthritis is time to observe the course of the patient. There are treatment implications to this time interval as well. Relatively nonhazardous measures may be evaluated and a comprehensive picture of the patient and his adjustment to various life situations obtained. Thus data may be accumulated with which to decide whether the risk of introducing more hazardous agents is war-

ranted. There is no evidence that this approach does harm in a chronic, slowly progressive disease, and it is invaluable in attaining for the physician the assurance with which he may remain unhurried and steadfast.

CLINICAL FEATURES

Certain salient features of peripheral joint rheumatoid arthritis deserve comment. It has a predilection for women (60–70% females), with incidence in people of all ages (1–96 years) but with the peak of the bell-shaped curve between 30 and 40. There is apparently no racial predisposition, but it seems to appear more frequently in the temperate zones where the more complex and exacting cultures exist.

NATURAL HISTORY. Several attempts have been made to study the natural history of rheumatoid arthritis. The most intensive study, at Massachusetts General Hospital (7–9), has the virtues that relatively few treatment agents have been used and patients have received very careful study, with emphasis on the concept of episodic vs. sustained disease and its corollary that episodic disease may be a frequent mode of onset and may develop in time into sustained disease (10). The only certain conclusion has been that typical disease sustained early in the course has a poor prognosis. In a study in our clinic, using liberal diagnostic criteria (11), many treatments were used and the follow-up between the original and final point of observation was often sketchy. The point in time approach was used to evaluate the functional status of the patient, since a continuous flow chart of the status of a group of patients presented a picture of utter confusion.

From these two studies, we have learned that about half the patients did well, a quarter poorly and a quarter remained the same. However, no attempt has yet been made, by either group, to assess pain relief, or the social and economic changes in a patient's status resulting from short-term management. These factors are important to consider in evaluating the success of palliation which, at present, is the goal of treatment, since a direct, curative approach is not yet available.

JOINT MANIFESTATIONS. *Clinical.*—In the overwhelming majority of patients, joint inflammation with its sequelae of pain, swelling, redness, deformities, and muscle wasting brings them to the physician. There seems to be a tendency for the small joints of the hand, notably the proximal

FIG. 1 *(above)*.—Characteristic hand deformities, joint swelling, muscle atrophy, ulnar deviation, and wrist fusion.

FIG. 2 *(below)*.—Location of the rheumatoid nodule.

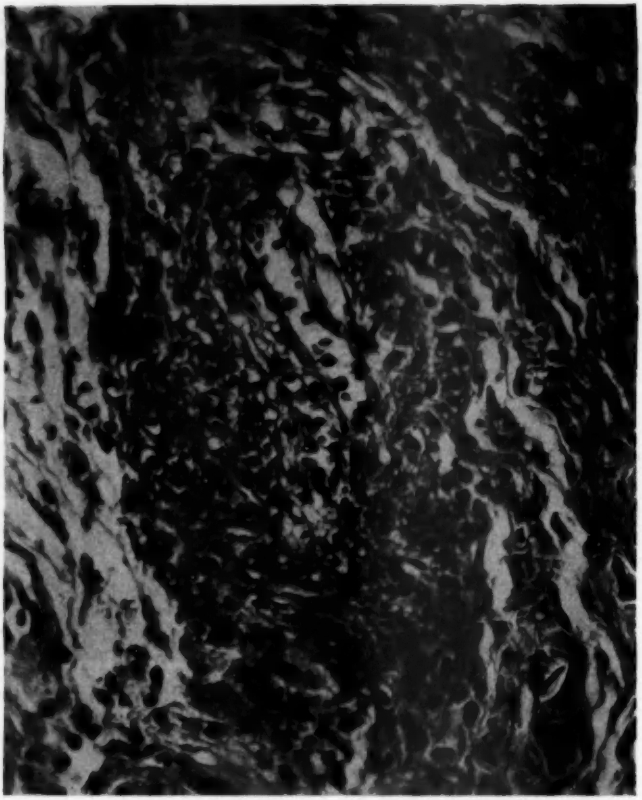

FIG. 3.—Rheumatoid nodule showing highly vascular granulations and necrosis of vessel wall; Masson trichrome.

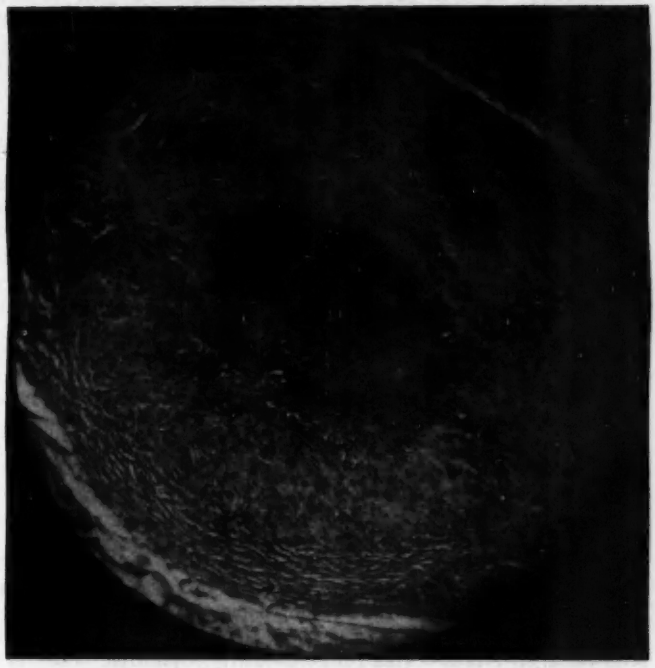

FIG. 4.—Rheumatoid nodule showing characteristic topography; hematoxylin-eosin.

interphalangeal and metacarpophalangeal joints, to be involved first, although almost any joint in the body may first be attacked. The small joints of the hands (excluding the terminal interphalangeal joints), wrists, shoulders, knees and feet are most often involved first.

The involved joint shows a fusiform appearance with swelling of the periarticular structures (Fig. 1). There is loss of mass in the muscles around the inflamed joint. The presence of inflammation, evidenced by heat, redness, or swelling, is variable. Tenosynovitis manifested by pain on passive motion referred to the tendon sheath is more indicative of a pyogenic arthritis—notably gonococcal—but it is occasionally seen in rheumatoid arthritis.

X-ray picture.—This varies with the intensity and sustained duration of joint inflammation. The earliest sign is soft tissue swelling only. This is followed by increased radiolucency of the bone adjacent to the joint margin, later including the shaft. Punched-out areas below the joint margin or loss of joint space may appear next and, ultimately, bony union may be seen. Uneven muscle forces, related to intrinsic muscle disease and involuntary splinting about an inflamed joint, lead to flexion contractures, ulnar deviation, and subluxations.

Synovial fluid.—Joint fluid is often increased in active disease. The cell content of the fluid mirrors the inflammatory process in the synovial membrane, and cell counts may vary widely, ranging up to 60,000 cells per cu. mm. with, at times, many polymorphonuclear leukocytes. Ordinarily, the cell count is lower with lymphocytes predominating. Cytologic study of joint fluid is rarely of great help in differential diagnosis since the rheumatoid process may at times provoke a polymorphonuclear reaction as great as a pyogenic stimulus (the gonococcus) or a lymphocytic reaction equal to that seen in a tuberculous joint. The protein content of the fluid is increased during inflammation, with elevated globulin concentration, but is of little assistance in differential diagnosis. Glucose concentration of the fluid may be low, but total absence of glucose does not necessarily imply bacterial invasion of the joint since this has been seen in rheumatoid arthritis, presumably related to the glycolytic activity of polymorphonuclear leukocytes.

The hyaluronic acid varies considerably in concentration and physical properties among patients and at times has the characteristics seen in normals. Study of these properties is rarely suitable for the clinical laboratory and in our hands has

seldom helped diagnostically, but is helpful as an approach to an understanding of the complicated mechanism of joint inflammation. Our feeling—probably oversimplified—has been that in rheumatoid arthritis, an excessive amount of imperfectly formed hyaluronate is produced during active disease. (See an excellent new monograph on synovial fluid (12) for further information.)

Pathology.—The synovial membrane shows inflammation, the intensity varying with duration and severity of the symptoms. These changes are nondescript; early, they consist of congestion and edema of the tissues below the lining membrane, with some cellular infiltration of polymorphonuclear cells. The lining cells degenerate and slough off, and granulation tissue appears. Later chronic inflammatory cells—lymphocytes, mononuclears and plasma cells—displace the polymorphonuclear leukocytes. There may be an occasional multinucleated giant cell. The synovial membrane becomes thickened in either a papillary or a villous form. The fiber bundles may show some "fibrinoid change." In a few instances, the picture of the rheumatoid nodule, discussed below, is seen in the synovia. The granulation tissue, known as pannus when it becomes less vascular, adheres to and extends into the articular cartilage from the joint surface and from beneath the subchondral plate. The subchondral granulation tissue may result in bone resorption with the x-ray appearance of punched-out areas. Adhesions between apposing areas of pannus or villous tufts result in fibrous ankylosis that may ossify and lead to bony fusion (13). Punch biopsy of the synovial membrane is relatively simple, but interpretation is unreliable because: (1) joint pathology tends to be nonspecific and accurate diagnosis from a small sample is difficult; (2) the lesions have a spotty distribution and a single punch may not represent the entire synovial picture. We prefer open surgical visualization if biopsy is required for diagnosis.

SKELETAL MUSCLE MANIFESTATIONS. Often the disease begins as an ill-defined muscle ache, and throughout its course, muscular symptoms are prominent. Muscle stiffness after inactivity is a common complaint—the most common according to some—and is almost the last complaint to disappear during a remission. No satisfactory physiologic explanation for this stiffness is known to us. Many patients complain of actual tenderness on palpation of certain groups of muscles. Muscle atrophy is frequent and flexion contrac-

tures are probably mediated through skeletal muscle imbalance. Increased electrical activity in the muscles adjacent to an involved joint (with a flexion contracture) has only been seen when the joint was passively extended beyond the limits of comfort. Some patients with marked muscle wasting or severe disease necessitating bed confinement may have increased urinary creatine excretion. Careful histologic examination of skeletal muscle has revealed small collections of inflammatory cells. The atrophy is easily visualized. The accepted explanation for the muscle atrophy—inflammation plus involuntary splinting of inflamed joints with consequent atrophy—is not satisfying.

NERVOUS SYSTEM MANIFESTATIONS. An occasional patient complains of paresthesias, but no clinical or electrical evidence for peripheral nerve involvement is usually found. Histologic examination has shown collections of inflammatory cells in the perineural sheaths in some patients, but the clinical-pathologic correlation is not well established. When peripheral nerves are involved, as in median nerve compression in the carpal tunnel syndrome, surgical decompression of the tunnel affords complete relief (21).

Muscle symptoms may be associated with features possibly related to hyperactivity of the sympathetic nervous system, manifested by moist, cool extremities, Raynaud's phenomena, and the hyperemia of the palms described as "liver palms." (This phenomenon is common with Laennec's cirrhosis, but its occurrence with rheumatoid arthritis does not indicate hepatic involvement.) The autonomic nervous system has been widely indicted with such catch phrases as "autonomic imbalance" or "sympathetic hypertonia." No one has yet described the pathways involved, and objective manifestations have not been modified by ganglionic blocking agents. In our clinic, a few patients have been subjected to sympathectomy. Their disease continued unabated although their hands were dry and peripheral arterioles remained patent during cold exposure. It is an attractive hypothesis but one difficult to study because of the lack of an approach.

THE RHEUMATOID NODULE. The frequency with which nodules are seen in patients with rheumatoid arthritis is directly related to the diagnostic criteria used to define the group. In various series, nodules have been noted in 10–20% of the patients. With rare exceptions their presence usually implies severe disease. The nodule has a fairly typical patho-

logic appearance, most specific for rheumatoid arthritis. An early rheumatoid nodule is indistinguishable to us from an old nodule in rheumatic fever, necrosis being greater and acute inflammation less in the rheumatoid nodule. Although several patients with typical nodules have developed SLE (positive L.E. cell preparation or the lesions of SLE at necropsy), we feel that these patients probably had both diseases. Histologic findings in rheumatoid arthritis, other than the nodule, are completely nondescript and could be produced by a simple chemical irritant such as turpentine. The nodules are almost never seen in ankylosing spondylitis, rarely in juvenile rheumatoid arthritis, and only occasionally in psoriasis arthropathica. Isolated reports have appeared stating that nodules have been removed from patients without other evidence of rheumatoid disease. We have not observed this. Serologic reactions are almost invariably positive in patients with nodules. Nodules appear over pressure points, in areas subject to mechanical stress or a shearing motion, over bones and joints, and at the roots and on the leaflets of the valves on the left side of the heart. The commonest site is juxta-articular, distal to the olecranon in the ambulatory patient or over the scapula or occiput in the bedridden one (Fig. 2).

Recently (13), a vascular basis as the site of the primary lesion for the morphogenesis of the nodule has been advanced, an idea originally suggested over 25 years ago (25). The primary lesion consists of very vascular granulation tissue, almost totally composed of blood vessels, lying in edematous connective tissue (Fig. 3). The arteriolar walls may be inflamed or necrotic, and fibrinoid material may be present. The cellular population ranges from chronic inflammatory cells to pleomorphic, occasionally multinucleated, connective tissue cells. Necrosis of tissue occurs. The "fibrinoid" material follows the planes of the collagen fibers, and at the margin, closely parallel layers of elongated cells are arranged radially in a palisade. With time, less vascular fibrous tissue surrounds the areas of necrosis, less fibrin-like material is observed in the necrotic area, and lipid deposition appears (Fig. 4). The end-result may be a sharply demarcated fibrous cyst containing grumous material. Areas of new nodule formation may occur side by side with an old cystic nodule.

HEART INVOLVEMENT. Most observers believe that clinical heart disease occurs at the same rate in patients with rheumatoid arthritis as in the general population. In patients

with rheumatoid arthritis who have come to necropsy the occurrence of heart disease morphologically indistinguishable from the scarred residue of rheumatic fever may be appreciably higher (66% according to one group).The lesions in the myocardium and valve leaflets may be the end-result of granulomatous inflammations similar to the subcutaneous nodule (1). They have also been seen in the epicardium associated with a pericarditis, which may explain the frequent finding of old pericarditis at necropsy (14).

EYE LESIONS. Iridocyclitis of varying duration and severity is seen in about 2% of patients with the peripheral type of rheumatoid arthritis. It is seen more frequently in spondylitis. The lesion is a nonspecific inflammatory one, and if of sufficient severity and chronicity may lead to blindness. Scleromalacia perforans is the end-result of a granulomatous lesion in the sclera similar histologically to the rheumatoid nodule, and herniation of uveal tissue may appear through the necrotic sclera. Sjögren's syndrome where an inflammatory process leads to atrophy and fibrosis of the lacrimal, salivary, and respiratory tract mucous glands is seen in a small number of patients with rheumatoid arthritis. The dry mouth, dry eyes and dry bronchial tree may lead to necrosis or infection. We have seen one patient whose death could be ascribed to frequent pulmonary infections and chronic pulmonary heart disease.

ANEMIA. Moderate anemia is common in active rheumatoid disease, correlating poorly with duration but to some extent with severity. It is of the hypochromic normocytic type usually associated with chronic inflammation or infection. Reticulocyte counts are usually normal and the bone marrow is essentially normal, but there may be an increased number of morphologically normal plasma cells. In a few patients, there is a significant decrease in red cell life span indicating a hemolytic component. In general, the serum iron level is decreased, the serum iron-binding capacity is normal, and the rate of radioactive iron incorporation into the red cells is within normal range (15). For lack of a better explanation, the anemia is probably of the hemolytic type with a decreased red cell life span and failure of the bone marrow to respond adequately to the protracted and excessive demand. The anemia responds variably to oral or intravenous iron but not to B_{12} or folic acid. It must be emphasized that a patient with rheumatoid arthritis may develop an iron deficiency anemia from chronic blood

loss, and this should not be overlooked. Reported increased efficacy of intravenous over oral administration of iron has not, in our experience, been confirmed. The dangers of homologous serum hepatitis overwhelmingly outweigh the possible temporary benefit from transfusions of whole blood or packed red cells, and transfusions are definitely not indicated in the treatment of this anemia. It is clear that anemia disappears when a remission ensues, however it may have been induced.

Splenectomy for the anemia alone is not helpful. In Felty's syndrome—severe rheumatoid arthritis with an enlarged spleen and pancytopenia—splenectomy may be considered as in other instances of hypersplenism.

MISCELLANEOUS CLINICAL ASSOCIATIONS. *Psoriasis.*—About 8% of patients with rheumatoid arthritis have psoriasis and, conversely, 1–2% of patients with psoriasis have rheumatoid arthritis. The psoriasis usually precedes the onset of arthritis but occasionally appears years after the development of sustained rheumatoid disease. In most instances, the arthritis is essentially similar to that seen in peripheral joint rheumatoid arthritis, but the serologic reactions are less frequently positive. Nodules are rarely seen in patients with psoriasis and arthritis. A few have the clinical peculiarity of arthritic involvement of the terminal interphalangeal joint when the nail of that digit is involved in the psoriatic process. Some feel that this clinical picture should be labeled psoriasis arthropathica. There is little correlation between the severity of the psoriasis and of the arthritis. Skin manifestations may not improve when the arthritis does (with cortisone administration) or vice versa (during the summer).

Myasthenia gravis; asthma; ulcerative colitis.—We have seen several patients with coexisting asthma and rheumatoid arthritis and a few with myasthenia gravis and rheumatoid arthritis. In some instances, the activity of the arthritis has subsided during an attack of asthma. Apparent clinical remission occurred during one episode of myasthenia that was difficult to manage. In our clinic patients with rheumatoid arthritis, a few have had ulcerative colitis at one time in their course, and 20% of a group with ulcerative colitis have had arthritic symptoms—more than half of these, arthralgias rather than typical rheumatoid arthritis. In most of them, as with those with psoriasis, there seems to be no correlation between activity of the colitis and activity of arthritis. Following total colectomy in two patients, arthritic symptoms have persisted.

Hay fever; urticaria; food sensitivity.—There has been no noted increased incidence of the common allergic disorders in patients with rheumatoid arthritis.

Cancer; diabetes; hypertension; peptic ulcer.—Of 374 patients carefully followed for more than five years, cancer appeared in about 2% and diabetes was known or appeared in 2% —probably not a significantly higher rate than in the general population. Hypertension (as determined by a casual blood pressure observation) was noted in about 9%, which is consistent with the age and sex distribution of the group. In this series, a proved peptic ulcer occurred sometime in the life of 2½%, but this figure must be qualified since it represents the patients who had sufficient symptoms to warrant a gastrointestinal series. Other groups have reported the incidence of peptic ulcer to be as high as 8%, but adequate data on the general population are not available for comparison.

Amyloid.—The incidence of amyloid increases with severity and duration of disease and the care with which amyloid is sought. Distribution is that of secondary amyloidosis involving liver, spleen, adrenals, and kidneys. When extensive, the primary type of amyloid distribution may be observed as well. Several case reports have documented gastrointestinal tract involvement with amyloid in patients with rheumatoid arthritis. The suggestion that cortisone treatment increases the incidence of amyloid has not been corroborated. As in other instances of amyloid secondary to chronic granulomatous processes, control of the inflammatory process would seem to be the best treatment. In one carefully studied patient in our group, we were unable to detect an appreciable change in amount of amyloid during 18 months of suboptimal cortisone therapy.

Gonads.—The ratio of sex incidence of peripheral joint rheumatoid arthritis in children is nearly one until puberty, when the relative proportion of females increases, augmented at the time of the menopause by a greater number of women to make the adult ratio of female to male, 2–2.5:1. These ratios are unexplained, but factors other than the relatively simple ones of estrogen, progesterone, and testosterone secretion are probably operative. Some have implied that adolescence is more trying for the female than the male and that the female menopause is also a strain. About the only solid bit of information available is that estrogen, progesterone, and testosterone administered singly or in combination in large amounts have

failed to influence the activity of rheumatoid arthritis. The relationship of sex to the incidence of rheumatoid arthritis remains unsettled.

Thyroid.—No reasons have been advanced to suggest that abnormal thyroidal function has a bearing on the disease. We have seen hyperthyroidism develop in about 3% of our patients during a five year period, and correction of this state with resultant euthyroidism has not changed the disease pattern. The converse has also been true with myxedema and its successful treatment.

Adrenals.—Despite the concept, suggested when cortisone was introduced as an antirheumatic agent, that this was a disease of adrenocortical insufficiency, no concrete evidence has been presented to show that the adrenal cortex in rheumatoid arthritis differs in any way from that seen in other debilitating diseases. Histologically and functionally it invariably responds adequately. We have studied one patient with Addison's disease and rheumatoid arthritis, and her disease was not unusual despite functionally complete absence of her adrenals. Patients with adrenocortical insufficiency maintained on desoxycorticosterone may develop aches and pains. This was at first ascribed to the peanut oil menstruum for the hormone, but the aches and pains persisted when pellets were used. This clinical picture, however, is nondescript, and we have yet to see such a patient develop the typical changes of rheumatoid arthritis.

Anterior pituitary.—There is no convincing evidence of abnormality of anterior pituitary function in rheumatoid arthritis. The arthritis seen with acromegaly is of the degenerative type, as is the arthritis produced in old rats by growth hormone. None of the sustained inflammatory characteristics seen in rheumatoid arthritis are found in these situations. In Simmonds' disease, rheumatoid arthritis is rarely observed, if at all.

Pregnancy and liver disease.—Many patients with rheumatoid arthritis experience a remission during pregnancy or during an episode of liver disease—particularly hepatitis. This has many of the characteristics of a cortisone-induced remission with a rebound following termination of the process and influenced Hench in his original decision to use cortisone in rheumatoid arthritis (16). The remission is presumably mediated through a hyperadrenal mechanism. In pregnancy, this results from overproduction of steroids partly by the placenta, whereas in hepatitis, degradation of steroid by the liver is supposed to be impaired (17). Because of the severe rebound post

partum, the presence of rheumatoid arthritis formerly was considered an adequate indication for interruption of the pregnancy. The rebound is equally severe following interruption as early as the third month. During disease activity, the presence of another child usually defeats the purpose of the regimen of decreased responsibility which we favor, and we would prefer that a woman with severe sustained disease not become pregnant when the disease is active. There is considerable difference of opinion on this point.

MANAGEMENT

Use of the term "management," rather than therapy, emphasizes our awareness that there is no cure and reminds us that active participation of the patient in the medical regimen undertaken is essential. Inherent in this term is the concept that measures are used to reduce the severity of the disease and to minimize the extent of irreversible damage during the period of active disease with the hope that a spontaneous or induced remission will ensue. It is desirable that this be achieved with a minimal amount of iatrogeny.

We have been developing the opinion that a variety of strains may influence the course unfavorably. This includes infection, trauma, as well as environmental stimulus resulting from economic, familial or marital relationships. To assess the significance of each of these, the physician must have a comprehensive view of his patient. This cannot usually be accomplished with one visit, even by the most perceptive physician, but requires seeing the patient over a period of time. This is not to say that classic psychoanalysis is suggested for every patient; but perceptive, astute listening may reveal significant strains. While this approach is being tried, the simplest treatment measures should be used, since these alone in combination with an interested physician may be sufficient.

As pressures are uncovered, attempts may be made to decrease them. Excessive fatigue is debilitating in a patient with rheumatoid arthritis. Brief rest periods during the day should be encouraged. Violent participation in community affairs, an extremely active social life, or the assumption of responsibility not immediately essential for economic or family survival should be modified downward. The essential responsibility load should be lightened, possibly with the aid of family and friends. An attempt is made to insulate the patient from the rigors of

the world. This should be considered only a temporary measure and can usually only be partially carried out in the most favorable circumstances. If the severity of the episode warrants it, a brief period of hospitalization may be desirable. This should not be confused with sanatorium care for 6–12 months. This is considered by many qualified people optimum treatment, but it is so financially impractical that it will not be discussed further.

PAIN RELIEF. Pain relief of some degree is the first aim in management and must be obtained before physical and functional rehabilitation can be considered. The pain is due to inflammation and, ideally, anti-inflammatory rather than strictly analgesic agents should be used. For this reason and because of the danger of addiction, opiates are seldom advocated. Codeine may be justified for short periods only. We assiduously avoid morphine, Demerol, and other opiates, as addiction can reasonably rapidly be induced.

Three groups of anti-inflammatory agents currently available are, in ascending order of potency, the salicylates, the butazolidin analogues, and the adrenal steroids. Butazolidin is unpredictable in its effectiveness in patients with peripheral joint rheumatoid arthritis. The hazards of administration are great, principally hemopoietic catastrophes, peptic ulceration, and sodium and fluid retention. For most, the hazards outweigh the possible benefits. We feel its use should be reserved for patients with gout and spondylitis where its benefits are likely to be greater.

Salicylates.—Salicylates are the drug of choice. Recently, aspirin has been more widely used than sodium salicylate. The advantages of one over the other are nebulous, but with present emphasis on sodium restriction, aspirin is possibly simpler to use. Aspirin will be discussed here, but the term can probably be considered interchangeable with sodium salicylate. Aspirin should regularly and frequently be administered throughout each day-night period in doses to the limit of tolerance and should not be given only "for pain." This is emphasized because we have frequently seen patients who were comfortable when aspirin was taken regularly but, when the drug was taken merely for symptoms, pain had been a major problem. A schedule of aspirin after each meal and at bedtime is a reasonable compromise with "regular frequent administration" that is compatible with daily living. Gastric tolerance may be increased by using coated aspirin or a buffered form. Some

patients become uncomfortably constipated with buffered aspirin, and enteric-coated should then be tried. Enteric-coating is not yet entirely satisfactory since many patients report passage of intact tablets through the gastrointestinal tract. This possibility should be explored before concluding that aspirin is ineffective in a particular patient. Para-aminobenzoic acid in 12 Gm. daily dosage increases the salicylate blood level. Smaller amounts have a minimum effect. We have found that it is simpler to increase the amount of aspirin than to use PABA. Commercially available combinations of PABA and aspirin have little to offer since the amount of PABA is too small to influence significantly the salicylate blood level.

Most of our ambulatory patients can take 2.4 Gm. (40 gr.) of aspirin daily—0.6 Gm. (two 0.3 Gm. tablets) after each meal and at bedtime. If gastric tolerance allows, this can be increased to 3.6 Gm. (60 gr.) daily. On an ambulatory basis, few patients can tolerate larger doses. Tinnitus in the ambulatory patient indicates the largest dose permissible since, without a change in dose, tinnitus may progress to deafness, and ultimately other manifestations of salicylism may appear before the next visit. In the closely observed hospitalized patient, tinnitus is an indication for increasing the dose to induce deafness, which is much less troublesome to the patient than tinnitus. The deafness induced by salicylates seldom leads to permanent damage except in acute salicylate poisoning. We do not believe that permanent deafness has resulted from the above regimen.

The addition of salicylate to the management program while the physician is learning the patient's story may lead to palliation which will satisfy both patient and physician. If this occurs, this course should be pursued indefinitely. If not, other measures should be considered. We usually begin gold therapy next, and if no benefit ensues after a complete course, adrenal steroids are used. For the sake of continuity, however, the steroids will be discussed next since their action is anti-inflammatory, whereas the action of gold compounds is not understood.

Adrenal hormones.—Cortisone was the first anti-inflammatory hormonal or steroidal agent introduced for treatment of rheumatoid arthritis. For the purposes of this discussion, it will be the prototype and the other agents will be discussed later. In most comments on treatment, prednisone can be substituted by the reader for cortisone.

Since Hench, Kendall, Slocumb and Polley (16) first tried cortisone and corticotropin in clinical medicine, there have been certain developments. (1) There is general agreement—for the first time—that the symptoms of rheumatoid arthritis are rapidly controlled by an administered agent. (2) There is controversy concerning evaluation of the effect on the disease of long-term steroid administration involving problems of criteria for diagnosis and evaluation of treatment. In every series of patients on sustained hormonal treatment reported to date, progressive joint damage has been documented in a large percentage (18, 19). (3) Most authors now feel that steroid treatment should be combined with the conservative management outlined previously. (4) The similarities between Cushing's syndrome and the syndrome induced by cortisone administration have become obvious (Table 1) (20). This has enabled one to predict certain undesirable features of cortisone administration. With increasing dose and/or prolonged cortisone administration, the patient shows more of the features of typical Cushing's syndrome. (5) Since cortisone modifies the host response and apparently does not influence the unknown offending agent, a clearer concept has developed of the components of the host response in rheumatoid arthritis. (6) Since cortisone has been shown to have anti-inflammatory and antireparative properties, it has become an excellent tool in study of the intermediate phases of these processes. Interest in the study of the dynamic phases of inflammation and repair has been reviewed. Thus, some of the untoward effects of steroid administration, including masking of infection, peptic ulceration, and osteoporosis, can be logically explained when related to total suppression of inflammation and repair. (7) The use of adrenal steroids has not aided in the search for an etiologic agent or agents, although a faint glimmer has been thrown on pathogenesis.

Certain general principles should be kept in mind when one considers the use of hormones in rheumatoid arthritis. The following discussion is permeated with personal opinions. The views presented are based primarily on clinical experience, for they are extremely difficult to study in a controlled clinical trial.

The concept of palliation must be constantly remembered. The complete restitution of a chronically ill person to total bodily and mental health is seldom possible. Practically, this means that the dosage of steroid which leads to a complete

TABLE 1.—Comparison of Findings in Spontaneous Cushing's Syndrome (20) and Long-Term Cortisone-Corticotropin Administration

Symptoms or Signs	In Spontaneous Cushing's Syndrome, 222 Cases (%)	In Long-Term Cortisone-ACTH Therapy (Av. 14.8 Mo.) 100 Cases (%)	In High-Dose* Therapy, 69 Cases (%)	In Low-Dose† Therapy, 31 Cases (%)
"Cushing" obesity	97	85	84	85
Hypertension or elevation of blood pressure	85	24	25	18
Menstrual disturbance; impotence in men	75	20	19	21
Hirsutism in females	70	40	39	42
Striae	68	3	3	3
Plethoric appearance	60	23	23	21
Weakness and backache	58	36	44	28
Mental symptoms	40	36	35	?41
Headache	39	8	7	11
Acne, pigmentation or other rash	37	15	13	20
Ankle edema	35	45	46	44
Poor wound healing or unusual infection	33	32	39	26
Purpura or easy bruisability	30	7	10	0
Polydipsia or polyuria	28	4	6	0
Glycosuria	27	6	3	10
Exophthalmos	7	0	0	0
Virilism	6	0	0	0

Others: Osteoporosis, peptic ulcer, spontaneous seizures

*525 mg. cortisone/wk. or over; 210 mg. ACTH/wk. or over.
†Up to 525 mg. cortisone/wk. or 210 mg. ACTH/wk.

symptomatic remission in a patient with severe disease is seldom tolerated for prolonged periods. The contrast of sustained and episodic disease must always be considered. If it were possible to predict that a patient with rheumatoid arthritis was in an episode and that withdrawal in the near future could be foreseen, steroid administration—with greater symptomatic relief—could be instituted less hesitantly. Since the end of an episode can never be predicted and since such unfounded optimism has led to nothing but trouble, we attempt to manage a possible episode with more conservative measures. When convinced that we are dealing with sustained disease, we then consider cortisone administration.

The rebound phenomenon should be remembered when

cortisone administration is contemplated. This phenomenon follows steroid withdrawal in certain patients with sustained disease. We have been unable to predict in which patient this will occur. It is essentially a transitory recrudescence of severe disease with widespread systemic involvement and, in the most violent form, can be fatal. The clinical manifestations are fever, tachycardia, weakness, the appearance of new areas of joint inflammation, serologic evidences of inflammation including a rising erythrocyte sedimentation rate, the appearance of C-reactive protein, hyperglobulinemia, and a rise in plasma fibrinogen. The rebound may be brief, lasting only a day or a week. In one patient it lasted a month, and resumption of cortisone administration was necessitated by her serious clinical state.

We believe that the method of withdrawal makes little difference in the type of rebound. When the dose is tapered slowly, the rebound develops at a given level, may be somewhat less severe but is as protracted and wearing on the patient as when hormone is abruptly discontinued. To insure an adequately functioning adrenal cortex during the rebound period, we have withdrawn most of our patients with concomitant corticotropin administration, and violent rebounds have been seen under these conditions, as well. The mechanisms involved in the rebound are not clearly defined. Our present naive hypothesis is that during steroid suppression of inflammation, material that completes the inflammatory process is stored and not utilized. When the steroidal dam is broached at withdrawal, this material floods the organism, leading to increased inflammation until the supply is exhausted. We know of no way to avoid a rebound except to avoid withdrawal when the disease is active.

The term "suboptimal" dosage has been defined as the dosage at which complete suppression of the inflammatory components of the disease is not obtained, but yet has some palliative effect. Since smaller doses of cortisone are employed, fewer complications of steroid treatment can be anticipated and a remission in the offing may be recognized. There is not agreement on the use of suboptimal dosage, complete symptomatic suppression being advocated by some. We feel, however, that untoward reactions with complete suppressive doses of steroid are so common that the risk is not justified. To avoid a rebound, cortisone administration should not be stopped when the disease is active. Two management implications stem

from this statement. *(a)* Don't start cortisone administration unless you are certain the indications for cortisone are present. Some of the most violent rebounds have followed cortisone withdrawal in patients started with inadequate indications. *(b)* If contraindications are present or may be anticipated, don't start cortisone.

a) Indications. The indications are not completely worked out. There are, however, certain fairly rational precepts that we tend to follow. We use the steroids as a last resort but do not wait until the patient has been devastated by the disease. Conservative management is tried first. If this results in partial symptomatic relief and an approach to adequate adjustment, we are generally satisfied. If, however, the process is rapidly progressive, remains sustained, and the patient is close to becoming incapacitated, cortisone administration is started. We have no alternative when the patient appears to be on the verge of being overwhelmed by a catastrophe. However, the comprehensive view of the patient continues to be as important to maintain when cortisone is being used. Some have said that steroid treatment increases joint damage since it allows the patient increased use of involved joints. The extreme alternative is complete withdrawal from life's activities—which often represents the greater evil. In addition, facilities for sanatorium care are not generally available, and some consideration must be given to the social and economic as well as to the anatomic and pathologic features of a patient's problem. If the principles outlined are followed, the indications for therapy will be defensible to the patient and the physician. The insignificant, though unpleasant, effects such as facial rounding, fat deposition, hirsutism, and acne should be explained to the patient. If a patient objects to hirsutism, he should probably not have been given cortisone in the first place.

b) Contraindications. *(1)* Age: One may anticipate more complications in the elderly patient. This, however, is not an absolute contraindication.

(2) Sex: The postmenopausal woman is apparently more prone to vertebral compression fractures. This, again, is not an absolute contraindication.

(3) Coexisting chronic infections: Bronchiectasis, chronic pyelonephritis, and the like constitute an absolute contraindication. Whenever our patients with these disorders have been given a steroid, it has been only a question of time before the infection has spread.

(4) Tuberculosis: Active tuberculosis is universally considered an absolute contraindication because of the almost absolute certainty of spread. Even apparently arrested and healed pulmonary tuberculosis of any extent is considered by many to be an absolute contraindication.

(5) Diabetes: This is more difficult to control on cortisone but is not an absolute contraindication. The indications must be very great to invite so difficult a therapeutic problem. Conversion of latent to overt diabetes by cortisone has been infrequent in our patients receiving long-term steroid administration.

(6) Peptic ulcer: This is a relative contraindication. Eighteen patients of our group of 68 on a five year study period of cortisone treatment developed a proved peptic ulcer. Thus, peptic ulcer may be anticipated in a high percentage of patients on long-term cortisone treatment.

(7) Mental aberrations: This is one of the major hazards of cortisone treatment. The following types have been observed: frank psychosis, either manic-depressive or schizophrenic; severe tension states; insomnia, and a reactive euphoria. In Cushing's syndrome, due to adrenal cortical hyperplasia or tumor, psychiatric difficulties are common. There is no agreement in the literature whether the pre-treatment personality characteristics permit prediction of psychiatric complications, and we also have been unable to predict the patient who will develop psychologic difficulties. We have had no experience with steroid administration in patients who have had a previous psychotic break because this has been considered a contraindication to treatment. However, a group of psychotic patients given large doses of corticotropin in an attempt to modify their psychosis developed typical Cushing's syndrome with marked edema and had no discernible modification of their mental state. In summary, a patient with rheumatoid arthritis who has had a psychotic break should not receive cortisone, and a few patients may be expected to show this reaction regardless of the care used in selection.

(8) Hypertension: There is no agreement concerning the advisability of beginning steroid treatment in a patient with pre-existing hypertension. A few patients in all series of long-term cortisone treatment have developed hypertension. Pre-existing hypertension may or may not be augmented during cortisone administration. The presence of hypertension with rheumatoid arthritis is considered a relative contraindication.

(9) Thrombophlebitis: We are not sure that the incidence of thrombophlebitis is greater in cortisone-treated patients with rheumatoid arthritis than in those receiving no steroid. These chronically ill people are prone to thrombophlebitis without cortisone. We have managed this complication with bed rest, elevation, and anticoagulants when indicated, and its appearance is not an indication for withdrawal.

(10) Convulsive disorders: A history of a convulsive disorder, in our opinion, is an absolute contraindication to cortisone treatment because of the tendency to induce status epilepticus.

When the indications for steroid treatment clearly outweigh the contraindications, when the patient will accept the minor untoward effects and the physician has the major complications in mind, when both are prepared for long-term treatment —then steroid treatment may begin.

c) Type of Hormone. A number of potent steroid preparations are available, and by the time this is published there probably will be more. Cortisone acetate was the first, and until recently oral cortisone was used most extensively. Corticotropin, despite the advantage of long-term effects produced by various gels and zinc preparations, has the disadvantage of requiring injection. Despite claims of its salutory effect compared with cortisone, this has not been apparent in our clinic. We have had patients taking corticotropin for four years, and their course has been similar to those patients taking oral cortisone. The disadvantage of the atrophic adrenal in patients taking cortisone is not great if this is constantly kept in mind, particularly during an emergency. For a time oral hydrocortisone alcohol was advocated because it was said to be more potent than cortisone and have fewer side effects. It does have about 1½ times the antirheumatic potency of cortisone acetate, but the side-effects are entirely similar to cortisone. Recently, the two medications have been used interchangeably in dose ratios inversely related to potency.

The 9-alpha halogenated steroids (9-alpha fluorohydrocortisone has been most widely used) have been recently introduced. Their potency is about 10 times that of cortisone, but marked sodium-retaining properties have made their use in rheumatoid arthritis impractical.

In the last year, the delta-1 steroids have been developed (22). These are known by several names, the accepted ones being prednisone and prednisolone. Insertion of a double bond

in the 1–2 position of cortisone or hydrocortisone to form prednisone or prednisolone, respectively, has increased the antirheumatic potency 3- to 5-fold. At doses required to control the symptoms of most patients, there is little or no sodium retention or potassium loss. Most patients require less than 30 mg. daily. At this dosage level, sodium restriction or potassium supplementation, often required with cortisone or hydrocortisone, is unnecessary. The other of the side effects appear similar to cortisone. During long-term cortisone therapy, about a third of our patients have developed edema necessitating salt restriction or diuretics. With the delta-1 steroids, it is anticipated that this will be necessary less often, and for this reason we feel that the delta-1 steroids represent the steroid of choice in long-term treatment. We are unable to detect a significant difference in antirheumatic potency or other effects between delta-1 cortisone (prednisone) and delta-1 hydrocortisone (prednisolone). In our clinic, many patients are seen who have had previous short trials of cortisone or hydrocortisone stopped because of the appearance of edema. This warning signal will be less evident with the delta-1 steroids, and the trend will therefore be toward greater antirheumatic suppression. If our thinking concerning the relationship between anti-inflammatory action and these other complications is correct, there will be a higher incidence of peptic ulceration, masked infection, and compression fractures (23). For these reasons, suboptimal treatment with the delta-1 steroids is re-emphasized. Recently, the 9-alpha fluoro delta-1 derivatives have been introduced. Although antirheumatic potency is high, the salt-retaining properties of the 9-alpha fluoro- compounds remain, and it is doubtful that these compounds will be useful in the management of rheumatoid arthritis and related diseases.

d) Route of Administration. Oral administration is undoubtedly the most feasible for long-term therapy. Orally administered cortisone or hydrocortisone is relatively rapidly excreted —within four hours. It is important, therefore, that the steroid be given frequently throughout the 24 hours. Every six to eight hours would be ideal, but this schedule is seldom compatible with daily living. Most of our patients have obtained relatively smooth symptomatic control by taking the steroid before each meal and at bedtime. In view of the fate of ingested hormone, it is obvious that the total daily dose should not be taken at one time, as with intramuscular cortisone. We see patients who had received steroid without benefit, but on closer

questioning find that the total daily dose was taken at one time. When the patient is unable to tolerate oral medication, cortisone acetate is given intramuscularly. This material is slowly absorbed and there is a lag between time of injection and effective action. However, its action is prolonged and an effect may be noted for as long as 60 hours after injection.

It is agreed that hydrocortisone acetate is at present the drug of choice for intra-articular use (24). By this route, symptomatic relief is much more constant than with cortisone. Intra-articular use of hydrocortisone remains a controversial subject. Undoubtedly, symptomatic relief is achieved in a large proportion of patients. The controversy revolves about the duration of relief and the impracticality of frequent, repeated injections. We have also observed a localized rebound in a joint injected intra-articularly with hydrocortisone following subsidence of the beneficial effect. In certain patients with one troublesome joint, intra-articular injection may be tried, though these attempts have not been too successful in rheumatoid arthritis.

Corticotropin gel is now used primarily to reactivate a cortisone-suppressed adrenal cortex before withdrawal of medication or before planned surgery. In our experience, 40 units daily, intramuscularly, for five days is sufficient to accomplish this; it is given concomitantly with the cortisone. Its antirheumatic action may last 12–48 hours, depending on the severity of the disease. Aqueous corticotropin may be given intravenously or intramuscularly. When given intravenously, maximal adrenal stimulation follows 25 mg. in 500 cc. of dextrose and water given in a slow drip during six to eight hours. We have been able to reactivate cortisone-suppressed adrenal cortices with such daily infusions for three successive days. Intramuscular injection of aqueous corticotropin is effective for only four to six hours. Destruction of the material by a peptidase in skeletal muscle is the presumed mechanism. It should be given in divided doses every six hours.

Hydrocortisone alcohol is moderately soluble in water, and a solution of 50–100 mg. in 500 cc. of dextrose and water may be given intravenously in a slow drip over six to eight hours or continuously during an emergency when adrenal reactivation has not been practical.

Large priming doses of hormone were originally advocated to obtain complete symptomatic suppression. With general abandonment of this goal, the starting dosage is lower, with progressive increase to the suboptimal level. In severe disease,

one usually starts with 20–25 mg. of prednisone daily, hoping adequate suboptimal therapy may be achieved at a top dosage of 25 mg. daily. With milder disease, correspondingly smaller dosage may be used.

e) Adjunctive Therapy. During hormonal treatment, the comprehensive approach should not be neglected. Many patients tend to overdo when pain is relieved by suppression of inflammation. This should be guarded against, and a patient should be encouraged to compromise with the demands of living.

It is generally accepted that salicylates should be used with steroids. The advantages of combined treatment have not been carefully documented, but in view of the small risk of complication with aspirin administration, it is probably warranted. We have demonstrated to our satisfaction that in most patients butazolidin given with hormone has not produced improvement beyond that with the hormone alone.

The suggestion has been made that gold therapy be started with cortisone administration. Cortisone would provide rapid symptomatic improvement, and when the gold-induced remission would ensue, the steroid could be withdrawn without fear of a rebound. The remission would be maintained with chrysotherapy. This would be ideal if remissions from gold were frequent enough. (This is discussed further on p. 34.) This regimen has been disputed on the basis that cortisone administered with gold would negate the possible beneficial effects of the gold, through mechanisms similar to those operating during cortisone suppression of its toxic effects. We have been unable to convince ourselves where the truth lies. It seems reasonable to try this combination and hope for the best. If a remission ensues, permitting cortisone withdrawal, a definite gain has been achieved. If not, and the indications for hormonal administration were valid, nothing has been lost. We are certain of two things: *(1)* a patient who has failed to respond to chrysotherapy maintains that resistance following a brief course of cortisone, and (2) the skin manifestations of gold toxicity are controlled by cortisone.

Some have advocated active measures to combat the tendency to demineralization and spontaneous fractures. These have included administration of a high protein, high calcium diet, strontium lactate, estrogens, and testosterone. Since it is extremely difficult with any regimen to induce a positive lime salt balance in a patient with severe rheumatoid arthritis

taking cortisone, not more than the simplest measures such as a high protein and high calcium diet seem indicated. Even these have not been widely used. Small amounts of gonadal hormones are worthless, have nuisance value, and are potentially toxic.

Because of the apparent tendency to peptic ulceration in a significant percentage of patients on long-term cortisone treatment, frequent feedings and the use of aluminum hydroxide antacids have been advocated, which seems reasonable. With frequent feedings, weight control—a difficult problem for patients taking cortisone alone—becomes doubly difficult.

A decreased uptake of radioactive iodine by the thyroid has been noted in a few patients on long-term therapy. The basal metabolic rate remains normal presumably because of the calorigenic effect of the adrenal hormones. This suggestion of induced hypothyroidism has led some to advocate thyroid medication for all patients receiving cortisone. Since adverse clinical effects have not been noted from the thyroid suppression and it is reversible when cortisone is stopped and occurs in only 5% of patients, we have not felt that thyroid medication is indicated.

f) Withdrawal and Surgical Emergencies. It must be emphasized that, when time permits, cortisone should be withdrawn with concomitant corticotropin. In an emergency, when time does not permit, one relies on depot intramuscular cortisone and intravenous hydrocortisone alcohol. It is a narrow channel between overdosage of hormone with its effects on inflammation and repair, and underdosage with its risk of rebound and addisonian-like crisis. From 50 to 200 mg. of hydrocortisone has been estimated to be required by the patient with Addison's disease in coping with the stress of a major surgical procedure. If adrenal cortical reactivation has been possible by corticotropin administration, the most refined procedure is to use aqueous corticotropin, intravenously or intramuscularly, during the critical period. This avoids the lag effect of intramuscular cortisone. More rapid changes can be made when employing aqueous corticotropin than with intramuscular cortisone. Intravenous hydrocortisone alcohol can be used with prompt response when there has not been time enough to withdraw cortisone and rapid supplementation of steroid is indicated. When there is little doubt that the patient can tolerate oral medication, oral cortisone should be started.

A rigid dosage schedule cannot be outlined for these emer-

gencies. The amount of hormone that will delay wound healing varies with the nutritional status of the patient, smaller doses having a significant effect in patients with poor nutrition. During the operative and immediately postoperative periods, need for hormone is greatest and concern with interference with wound repair is less. Large amounts of hormone, probably larger than required—200–300 mg. of cortisone or hydrocortisone or 100 units of corticotropin daily—may be used on the day of operation and the first postoperative day. By the third day, we reduce this to 50–75 mg. of oral cortisone or 10–15 units of corticotropin—the latter only if the patient is unable to tolerate oral medication. At these dosages, we have observed no difficulty with repair of skin or bone defects regardless of nutritional status, but in a poorly nourished patient, an intestinal anastomosis has occasionally broken down. Therefore, after bowel anastomosis, we carry the patient through the critical period as outlined above, and withdraw all hormone on the third or fourth day, suffering a rebound if such develops as a necessary evil. Two or three weeks later, when firm closure is reasonably assured, hormone is resumed if indicated. Using this regimen in cortisone-treated patients subjected to surgical procedures, we have not had a sudden death, as has been described by others. Careful postoperative care is necessary, with constant supervision and willingness to vary the dosage of hormone with changing conditions. Obviously, in the face of an acute surgical problem, the possibility of the patient's taking cortisone or an allied hormone must be established so that measures can be taken to prevent catastrophe.

g) Management of Complications. These have been mentioned in various other sections, but their importance warrants some repetition.

(1) Infections: With the suboptimal dosage regimen, most infectious processes will produce some symptoms, but these may be masked and quite bizarre. Any symptom suggesting infection should receive a complete work-up including a blood culture. When a pyogenic infection is strongly suspected or confirmed, the patient should receive bactericidal antibiotics (shown to be as effective in cortisone-treated animals as in controls). With bacteriostatic agents, cortisone treatment may increase the mortality. We combine penicillin and streptomycin for pyogenic infections before cultures have been made and give the broad spectrum antibiotics only when a specific

potent sensitivity to a particular agent has been demonstrated. Viral infections, without effective antibiotics, present a real challenge. The usual childhood diseases may seriously threaten patients during long-term cortisone treatment: at least one death from chickenpox has been reported. We hospitalize these patients and reduce hormone dosage below that required for suboptimal maintenance. Vaccination with vaccinia virus in a cortisone-treated patient should not be undertaken lightly. Vaccinia dissemination has been observed in man under these conditions. Wide dissemination of the virus occurs in cortisone-treated animals without the appearance of a skin lesion. In summary, infectious processes during cortisone therapy must be discerned under the mask of cortisone and should be treated promptly by available specific means. If none are available, lowering the dosage must be considered. When the infection has a poor prognosis and is not amenable to bactericidal antibiotic therapy, withdrawal of steroid treatment is imperative.

(2) Peptic ulcer: This may be anticipated in a significant percentage of patients on long-term cortisone treatment, but symptoms may be minimal or absent. We do not know if development of a peptic ulcer in a patient who cannot be denied long-term cortisone treatment constitutes an indication for surgery of the ulcer. The indications for surgery for this group are similar to those for the patient who is not receiving cortisone. Sufficient data to show that the postgastrectomy cortisone-treated patient has a decreased tendency to recurrent ulcer are not available. Obviously a perforated ulcer is an excellent reason for surgery. The incidence of gastric, in contrast to duodenal, ulcers in our long-term cortisone patients is 50% —apparently higher than in general. With medical management of the peptic ulcers of cortisone-treated patients, the healing rate has been slower than one usually hopes for in a gastric ulcer. Two subjected to partial gastrectomy for this reason showed no carcinoma. One refused operation and subsequently healed. None of our patients with a proved ulcer has had perforation. Two perforations have appeared suddenly, without the warning of previous ulcer symptoms.

(3) Osteoporosis and pathologic fracture: There is no known prophylaxis, but patients should be encouraged to be as physically active as tolerable within limits of the compromises previously stated. Our patients are encouraged to eat a high protein, high calcium diet. No accurate measurements

of bone radiodensity are available, but casual comparison of roentgenograms shows that most patients develop an increasing radiolucency during a period of years on cortisone. We have been able to correlate the development of pathologic fractures with the postmenopausal state, with physical inactivity consequent to a bed and chair existence and, lastly, with very large hormonal dosage (26). The occurrence of a vertebral compression fracture with back or root pain is a difficult situation. Ideally, hormone should be withdrawn, a suitable brace applied, and the fracture allowed to heal. However, with hormone withdrawal and possible rebound, the patient may become bedfast, scarcely optimal for promoting the healing of osteoporotic bone. We are not yet convinced of the proper course. Prophylaxis by proper selection of patients for hormone treatment is a more reasonable approach. Gonadal hormones and strontium lactate have not consistently produced positive lime salt balance. Several of our patients who could not tolerate the rebound following withdrawal have been maintained on cortisone and symptoms referable to the compression have subsided. We have seen no neurologic catastrophes, such as cord transection, but further collapse has been noted in one patient.

(4) Psychiatric difficulties: Excessive euphoria and insomnia usually only require a small decrease in dosage or increased sedation. Anxiety and tension states may necessitate expert psychiatric help, in addition to the general supportive role of the physician. The decision to withdraw cortisone should be made in consultation with the psychiatrist. In our experience, chlorpromazine and Rauwolfia preparations have not been helpful in patients with rheumatoid arthritis (this contrasts with our experience with SLE when chlorpromazine has been quite useful in similar circumstances). With a frank psychosis, cortisone withdrawal with concomitant corticotropin is indicated. It is essential that these patients have psychiatric supervision with constant observation to prevent suicide. Frequently, our psychiatric consultants have been forced to resort to electroshock treatment to control a debilitating manic reaction. It has been noted that after cortisone withdrawal, the erythrocyte sedimentation rate rises and objective changes of active arthritis appear, but subjective symptoms of a rebound tend to be minimal until the mania has subsided. Caution should be exercised with shock treatment of these patients with osteoporotic bones, to prevent fractures—particularly of the ver-

tebral bodies—during the convulsion. We believe that a psychosis induced by cortisone in rheumatoid arthritis constitutes an absolute contraindication to the reinstitution of hormonal therapy.

(5) Sodium retention and edema: Edema has appeared in at least a third of our cortisone-treated patients. Steroid administration need not be stopped, because salt restriction, mercurial diuresis, and occasionally digitalization control this complication satisfactorily. Since mercurial diuretics potentiate the tendency to hypokalemia with cortisone administration, dietary potassium should be supplemented. Enteric-coated potassium chloride tablets, 0.9 Gm., three to four times daily have regularly controlled this tendency in our cortisone-treated patients. Our patients receiving long-term cortisone treatment have not required supplemental potassium in the absence of mercurial diuresis.

With prednisone, this feature of steroid treatment has been less prominent. On all reported balance studies, at dosage levels of 30 mg. or less of prednisone daily, no significant sodium gain or sustained potassium loss has been observed. This is probably the sole advantage of this steroid. When our patients were transferred from cortisone to prednisone, a liberal sodium intake was permitted. On this regimen, three patients developed edema on dosage of 25 mg. or less of prednisone or prednisolone, necessitating resumption of sodium restriction. We have no reason to believe that these patients have any medical complication predisposing them to salt and water retention. We have no explanation for this observation, particularly in view of the balance data cited above.

(6) Hypertension: This complication developing with cortisone treatment has been of some concern to us. We have been forced to withdraw hormone administration from three patients because of development of severe hypertension.

(7) Diabetes: During cortisone treatment the appearance of diabetes is considered to represent the unmasking by cortisone of a latent tendency. There is no tendency to ketosis and the diabetes should be managed in the usual manner. If it becomes resistant or too brittle, this is an indication for withdrawal and a contraindication for resumption of cortisone.

CHRYSOTHERAPY—GOLD COMPOUNDS. The evaluation of chrysotherapy in rheumatoid arthritis is an almost insoluble problem. No agreement exists concerning the use of gold in management of the disease. This confusion is due

primarily to the difficulties inherent in evaluating treatment in a chronic disease that appears at times in a self-limited episodic form. There are a few points to be made: *(1)* Every patient with rheumatoid arthritis does not experience a remission following the administration of gold. *(2)* Patients with well-documented sustained disease have had remissions following gold administration. *(3)* The "course" regimen, in which gold is given weekly for a period and then stopped, leads only to temporary remission in most patients (27). No satisfactory studies document the value of long-term maintenance treatment with gold. *(4)* Toxic reactions to gold compounds are common and a major nuisance, but they are seldom fatal and usually are controlled with cortisone.

We are on the fence in the controversy over chrysotherapy. In the past, we have said, without absolute certainty, that gold leads to a temporary remission of rheumatoid arthritis in some patients, and we still believe this. This seems to be in accord with the observation that not all patients have remission of their disease. We cannot be certain of the value of maintenance treatment. Since the toxic reactions are usually a nuisance and not serious, we use gold when indicated and, with significant clinical improvement, continue a maintenance regimen in the hope that the remission will persist.

The *indications* for gold are simple. If the disease cannot be controlled with conservative measures, gold should be considered. The suggestion that gold and cortisone be started together in the hope that when the beneficial effects of gold become apparent, cortisone may be withdrawn, is difficult to evaluate. We prefer first to use gold alone, in the hope for success without the use of cortisone. Where disease progression is extremely rapid and the course very unfavorable, the combination may be tried.

There are definite *contraindications* to the use of gold compounds, based on toxic reactions encountered. These primarily involve three systems: *(1)* skin and mucous membranes; *(2)* hemopoietic; *(3)* renal.

(1) Skin: All pruritus developing during gold therapy should be presumptively causally related. The gold should be withheld immediately. The slow renal excretion of gold that persists for months (28, 29) raises the possibility that a toxic reaction will persist for months. The skin lesions vary from transient itching to exfoliative dermatitis. The most minor reactions may subside with the stopping of gold treatment.

The less severe ones frequently respond to local treatment with the usual antipruritic salves or lotions. The most severe require treatment with BAL or cortisone. There is fair documentation that BAL will counteract most of the severe skin reactions. Its action is not completely understood, however, since a relatively small percentage of the retained gold is excreted during BAL administration. When the patient is in a remission from arthritis, BAL is the treatment of choice. Its administration has the hazard of injection abscesses and hypotensive syncope. The latter may be controlled by ephedrine. The extensive reaction to gold may require protracted hospitalization for BAL treatment. The versenes have not been adequately studied. If the reaction to gold is severe, if the arthritis is not in remission, or if BAL is ineffective, cortisone should be used. We have not seen a skin reaction ascribable to gold that has not responded to cortisone. When the reaction is localized, 1% hydrocortisone lotion or 0.25% 9-alpha fluorohydrocortisone lotion controls the symptoms, thereby avoiding the hazards of systemic steroid treatment.

Stomatitis, similar to that seen with other heavy metals, may require treatment as described for the skin reactions. A metallic taste is common but is not an indication for stopping treatment. Gold colitis has been reported, but we have never seen this complication.

(2) Hemopoietic reactions: These consist of a depression of one or more elements of the bone marrow. They are seen less often than formerly. Pancytopenia with an aplastic picture, thrombocytopenia, agranulocytosis, and a progressive anemia of unknown etiology have been described. Some of these patients may represent unrecognized SLE. Some probably represent the unwise use of gold; e.g., aplastic anemia developed in a patient receiving extensive radiotherapy for cervical carcinoma, in addition to gold. The hemopoietic reactions have been reported to respond poorly to cortisone administration.

(3) Renal complications: These are due to a heavy metal type of nephropathy. Transient hematuria is occasionally seen, and in rare instances a nephrotic syndrome develops similar to that seen with other heavy metals. These renal complications appear infrequently, but the urine should be examined regularly during gold therapy for protein and abnormal microscopic elements. The abnormality has disappeared with

the cessation of gold, and BAL or cortisone has not been needed in our patients.

Several other presumed toxic reactions to gold are based on tenuous evidence. A toxic hepatitis has been described that, in retrospect, was probably due to homologous serum hepatitis from contaminated syringes. There is one report of a patient in whom cholangiolitic hepatitis appeared early in the course of gold treatment and resembled that seen following arsenicals. It is extremely rare and presents no major problem.

Systemic lupus erythematosus has been considered a contraindication to gold therapy because it is ineffective in this disease. It has been suggested that gold acts as a sensitizing agent and that one may explain on this basis the frequency with which SLE develops in patients with chronic rheumatoid arthritis. We do not agree, since we have seen no evidence to support it in a study of the natural history of rheumatoid arthritis, gold-treated patients or long-term cortisone-treated patients—87% of the latter group had had gold in the past.

Some have thought that the beneficial effects of gold appear only in the patient who has had a toxic reaction, but there are numerous exceptions—patients with severe skin eruptions who have not gone into remission, and remissions without toxic reactions.

Because of the toxic reactions, one should hesitate to administer gold to a patient prone to pruritis eruptions, with renal disease, with a depression of circulating blood cells, or possibly with liver disease. As a corollary, one should hesitate to use gold in combination with agents that tend to depress the bone marrow such as butazolidin or radiotherapy, or with hepatotoxic agents such as cinchophen. Systemic lupus erythematosus should be excluded as far as possible. These represent, we feel, the sole contraindications. This contrasts with the contraindications to cortisone treatment.

It is gratifying for patient and physician when a gold-induced remission develops, for management is greatly simplified. The disease process as far as can be determined is quiescent, not suppressed. Visits may be infrequent and the responsibility load of the physician is lightened. The attainment of this desirable result warrants the assumption of the slight risk of gold treatment in the selected patient.

Practical considerations.—For gold to be effective, it must be combined with a thio- group, possibly needed for solubility at the body pH. The colloidal gold preparations cause no tox-

icity but are ineffective since they are taken up completely by cells of the reticuloendothelial system. Numerous preparations are available under various trade names. Some are for intravenous use only, which makes chronic administration difficult, and intramuscular preparations are more practical to use. Some are prepared in menstruums that slow absorption. In view of their extremely slow excretion, the use of slow absorption preparations seems to have no rationale. These gold preparations are loosely referred to as gold salts, but should be called gold compounds. Aurothioglucose, aurothiomalate, and aurothiosulfate are most commonly used, and at present no differences are apparent among them. They contain between 40 and 50% metallic gold.

Dosage schedules vary widely. In most clinics, small doses are used at the beginning—10–25 mg. of the compound weekly for one to two weeks. Previously, 100 mg. a week was advocated but toxic reactions were frequent. They seem to have decreased since the weekly dose has been cut to 50 mg. This amount is usually employed, but some have advocated smaller amounts, 25 or 10 mg. a week. On the continent, clinicians suggest 400–600 mg. a week. We have had no experience with the very large doses. It hardly seems necessary to state here that when the effectiveness of gold is so difficult to evaluate, discussion of the value of different dosage schedules hardly seems worth while. In this country the course method—weekly administration to a total of 1–2 Gm. with a free period of several months and then another course of 1–2 Gm.—has been abandoned in favor of maintenance dosage. Our program consists of giving 50 mg. weekly until a remission ensues and then beginning a maintenance schedule of 50 mg. every two to three weeks, depending on the clinical course. If no remission develops after a total of 2,000 mg., gold therapy must be considered a failure and is stopped. If a toxic reaction develops, gold is stopped, temporarily for a minor reaction, permanently for a severe one. The patient is seen by a physician before each injection and questioned particularly regarding pruritus and stomatitis. Complete blood counts with an estimation of platelets on the smear and a urinalysis for albumin and microscopic study are done at three-week intervals. The development of marked eosinophilia may, but does not always, presage a skin reaction. Gold is stopped if any abnormalities of blood or urine appear.

PHYSICAL THERAPY. The role of physical medicine

in management of rheumatoid arthritis deserves some comment, and we believe present concepts need re-evaluation. There is no agreement concerning the exact role of this discipline. We are certain that most of the complex machines used in this specialty have little effect on the disease. They are expensive, require transportation of the patient, and often the effort consumed in the trip from home to gadget negates any possible benefit to be derived from it. We are not convinced that on an in-patient basis diathermy, ultrasonics, whirlpool baths, or massage have a place in the management of rheumatoid arthritis. There is good evidence that exercises against resistance will overcome the protein catabolic effects of the disease and associated physical inactivity. Such exercises cannot, however, be carried out regularly until pain is at least partially controlled. If exercises are performed beyond the limits of minor fatigue, the following day is likely to be difficult for the patient, with increased pain and stiffness. The major function of exercise is to re-establish, if possible, functioning muscle mass. Passive exercises, if carried out daily, may prevent fusion but accomplish little or nothing toward muscle strengthening. They should be regarded as temporary measures during very acute disease, progressing then to active exercises against increasing amounts of resistance as control of the disease is achieved. Exercises may be more easily performed in a warm atmosphere and under water. The availability of a suitable pool constitutes the indication for its use. If an arduous trip is required to carry out exercises under water, the pool should be avoided. If it can be done without undue hardship, it is worth while. Stretching exercises have not been successful in our hands for a protracted period unless they are regularly and conscientiously continued. As you are probably tired of hearing, this is a chronic disease, and if disease activity is sustained, measures to modify it must be continued during the period of continued activity. When disease activity may persist for years, a program of exercises becomes a distinct chore.

DEFORMITIES. *Development and prevention.*—In the extensive literature on prevention of deformities—primarily flexion contractures—many points of view have been expressed, varying from the pessimistic extreme in which joints are encouraged to fuse in the position of optimal utility, to the overoptimistic in which the development of any deformity is considered a reflection of the capability of the physician. Sup-

pression of disease activity remains the aim, and with partial pain relief, functioning muscle mass may be restored with resistance exercises. Positions of rest favoring the production of flexion contractures should be avoided. This applies principally to the knees, which should be kept extended at rest without the comfort of a pillow beneath them. If the factors leading to deformities are controlled, their development may be modified. Constant supervision and awareness of the continuing danger of deformities is needed. The patient should be encouraged to carry his joints through a full range of motion daily and, if difficulty is noted in doing this, mild stretching exercises slightly beyond pain limits should be started. The only practical method is to enlist a member of the family to supervise these exercises. This individual needs careful indoctrination and dogged persistence to bear the weight of this responsibility day in and day out, perhaps for years. Without such a person, the program is rarely feasible, since daily physical medical care is seldom practicable in the home and transportation difficulties associated with daily clinic physiotherapy in most instances make it valueless.

The use of rest splints—molded half-shells—to prevent deformities, is advocated in all the standard texts but needs reappraisal from the point of view of simple common sense. Most patients stop wearing a splint after varying lengths of time, usually within weeks. The smaller and lighter the splint, the longer used. These molded shells need frequent revision, constant remodeling and upkeep attention by the physician, and constant supervision by the person in the home assigned to the supervisory job. It again becomes a tedious chore. Circular plaster without bivalving should be avoided for more than a day or two unless fusion of a joint is desired, since muscle atrophy induced by continued immobilization in plaster defeats the basic purpose of the program, i.e., to re-establish muscle mass. In summary, therefore, common-sense measures regarding positions of rest, stretching, and resistance exercises constitute the major efforts toward the prevention of deformities. Rest splints, in our opinion, play little or no role in this program. With these means, deformities may be prevented in some, minimized in others, but will develop in a few, when supervision becomes less rigid because of boredom or other interfering situations.

Correction.—Many methods for the correction of deformities have been suggested. Stretching exercises beyond pain

limits play a role only in the prevention of deformities. Manipulation under anesthesia rarely accomplishes anything worth while in severe disease, since the resultant trauma sets up a reaction which negates a possible benefit. Wedging casts have the specific disadvantage of prolonged immobilization with resultant muscle atrophy, possible fracture of osteoporotic bone, and subluxation of involved joints. Skeletal or skin traction has not been found satisfactory by most. In most knee flexion contractures of any duration, the posterior joint capsule has been shortened, and if enough traction is exerted to straighten the knee, the tibia will become subluxated on the femur. If a flexion contracture is overcome, joint motion, as well as the position of increased extension, must be maintained.

Finally, various arthroplasties have been devised and advocated for correction of deformities. Although the immediate postoperative result may be beautiful to behold, this is of small importance in this chronic disease. Basic tenets must continually be kept in mind. For instance, for an optimal result in the knee, maximal active joint motion with extension to beyond 180°, relative freedom from pain, and a stable joint must be obtained. This requires a vigorous postoperative program of exercises to insure full range of motion and re-establishment of muscle strength, to be continued throughout the period of disease activity. Some suppressive therapy is also required to control pain if the disease remains active. We are trying to make the point that in the presence of active disease, orthopedic intervention with splints, traction or operatively is but the beginning of a long, hard road. To undertake this without a clear understanding by patient and physician of the time and effort involved is unfair to both. Only if one is aware of the effort involved in the full program and if continued supervision is guaranteed, may it be undertaken. Only a few of our patients or their families have had the stamina to continue it. Patients with arthroplasties for functional improvement in the upper extremity seem to do better with a less arduous postoperative course, probably because there are no problems of weight-bearing. A few courageous souls have considered reconstructive surgery of the hand, but these procedures are still in the experimental phase.

Joint fusion by operative means deserves more attention than it has received. A stable painless joint is the result. However, since a patient may carry out daily living functions with

one fused knee but will be severely handicapped with two, the unoperated knee must be fairly free of disease before knee fusion is considered. In the foot, fusion is often the operation of choice, and a talonavicular fusion in the selected patient may be very salutory. Wrist fusion has also been followed by considerable benefit in selected patients.

Rehabilitation.—Total rehabilitation as applied to the patient with rheumatoid arthritis is a relatively new interest (30). For the first time, rehabilitation has been applied to a dynamic disease and not to the static end-results of a damaging process. In addition to its dynamic nature, rheumatoid arthritis presents the problem of pain. A patient rehabilitated to live with one damaged knee may fail when pain develops in the opposite knee. Impressive, temporary results have been obtained using all the modalities outlined under management plus specialized rehabilitation techniques. The patient must be well motivated to desire rehabilitation, and proper motivation has been difficult to predict. Costs of the full program are exorbitant and in most instances have required public funds. Adequate reports of only a short period, at the most two years, are available, and the feasibility of the program with its high cost and great expenditure of time and energy per patient depends upon the durability of the good results. Further follow-up results on this program are awaited with interest, but, as in any regimen advised for rheumatoid arthritis, heroic measures should not be undertaken lightly. A real injustice may be done to the patient who has made a good adjustment to a difficult handicap when his improvement, requiring vigorous measures, is only temporary. He frequently must again go through the difficult readjustment process.

SUMMARY

To summarize the general principles outlined here, this is a disease with wide variation in severity and unpredictable course. During the episodic phase, simple palliative measures only should be used. During sustained disease, more hazardous attempts to control the disease or at least partially to suppress its unpleasant features, most of which stem from pain, are indicated. Treatment potency and hazard to patient seem to go hand in hand and in ascending order may be grouped as follows: *(1)* modification of patient's life situation; *(2)* salicylates; *(3)* chrysotherapy; *(4)* hormones.

The simplest and least hazardous techniques should receive adequate trial before the next most potent is considered. How long each trial period should be depends on the rate of progression of the disease and social and economic factors in the patient's life situation. Precipitate action without due consideration of the many factors involved should never be undertaken. Lack of steadfastness can do harm in certain instances but, when no harm is actually done, can confuse the patient, prolong his misery, and cost him money. We are dealing with a chronic disease that requires continuing supervision for years, regardless of the status of disease activity. One must be ready to change the degree of patient activity permitted and the amount of suppressive medication administered by small increments, dependent on the patient's status. Nothing should be done abruptly; management must be fluid. Heroic measures should be undertaken only with the full knowledge of the patient and family with regard to the amount of effort required from them for successful completion of the endeavor. When sustained disease has been present for years and the patient is well-adjusted to a restricted life, violent disruption of that life situation should not be undertaken lightly and, until present studies are completed, we believe should not be undertaken at all in the most severe situations. Small degrees of improvement are likely to be enjoyed for longer periods of time than are abrupt and miraculous cures.

Comments referring to severe sustained disease apply only to 10–15% of patients. The great majority, if one is liberal in diagnostic criteria, do quite well and carry out their life functions with only partial restrictions. The physician should advise them concerning these restrictions and attempt to relieve pain and prevent deformities. This concept of palliation is important: one may with assurance tell the patient that the severity of his difficulties may be decreased, but in relatively few instances may one anticipate their complete elimination.

APPENDIX I. JUVENILE RHEUMATOID ARTHRITIS (STILL'S DISEASE)

Certain differences exist between adult rheumatoid arthritis and the disease when it appears before puberty. The juvenile form, although seen less frequently than the adult, is not a rare or exotic disease; it represents 6–10% of our patients with rheumatoid arthritis.

Clinical manifestations.—The illness began at age 9 months in one of our patients. The sex ratio is more nearly equal when the

disease appears before puberty, most reports citing a ratio of 1.5 females to 1 male. Characteristically, changes in growth and development appear. When the inflammatory process involves joints in relation to open epiphyseal centers, they may respond with increased growth and premature closure. The end-result is related to age, so that growth temporarily increases but ultimately shortening of the bone adjacent to the involved joint is the result (Fig. 5) (31). Micrognathia occurs because of growth disturbance, but the mechanism is not clear since it may develop without obvious involvement of the temporomandibular joint. Apparently some growth of the mandible takes place from membranous bone at the center of the arch.

Terminal interphalangeal joints may be involved, in contrast to the adult form where this is usually seen with psoriasis of the nail of the affected digit. The cervical spine may be fused in a characteristic fashion, and many of our patients with severe juvenile rheumatoid arthritis have sacroiliac changes that on x-ray films are indistinguishable from those seen in rheumatoid spondylitis but without a stiff lumbar spine. Nodules typical of adult rheumatoid arthritis are rare in the juvenile form. A common onset in the juvenile form is high fever without evidence of arthritic involvement for weeks or even months. Another onset frequently seen is chronic large joint monoarticular arthritis.

Laboratory findings are similar to those seen in the adult form except that the serologic reactions—streptococcus agglutination and sensitized sheep cell reaction—are usually negative.

In children, an important point of differential diagnosis, seldom encountered in adults, concerns distinguishing the single joint, so frequently seen at the onset of the juvenile disease, from tuberculous arthritis. If the tuberculin reaction is positive, we do an open joint biopsy for section and culture of tissue for acid-fast bacilli. Since specific therapy is available for this infection and the joint damage is directly related to the duration of infection, early diagnosis is essential.

Management is similar to that advocated for the adult form. Studies of natural history involving large number of patients are few. Several have presented widely divergent views of the anticipated prognosis. These differences are probably due to differences in patient population from which the study has been derived. When patients with severe disease have been studied, the end-result has been grim. One study that concluded that these patients had a poor prognosis appeared from a special hospital—the Robert Breck Brigham (32). Patients admitted to this hospital represent the most severe form of the disease. The study of juvenile rheumatoid arthritis carried out in our clinic 10 years ago (33) revealed a much happier prognosis; diagnostic criteria were quite narrow. We are conducting another examination of our patients with juvenile disease, using a liberal diagnostic approach that includes all children

FIG. 5.—Changes in growth—overgrowth and stunting—seen in juvenile rheumatoid arthritis.

with more than one joint involved for at least two months. With these criteria, our preliminary impression of the prognosis is excellent with simple measures. Upper respiratory infections, particularly streptococcal, represent a frequent traumatic incident in childhood. For this reason, we have had a group of these patients taking sulfadiazine prophylaxis similar to that used in rheumatic fever. It has seemed a logical procedure with minimal hazard, and our impression—not well documented—is that it is worth while. Except for sulfadiazine prophylaxis, the management of the disease in children is similar to that in adults.

APPENDIX II. RHEUMATOID SPONDYLITIS

This entity (also known as Marie-Strümpell or ankylosing spondylitis) is considered by some a variant of rheumatoid arthritis, by others a separate and distinct disease. The former base their opinion on pathologic similarities and the well-documented observation that the peripheral joint involvement is clinically indistinguishable

TABLE 2

	Marie-Strumpell Spondylitis	Peripheral Joint Rheumatoid Arthritis
Sex incidence	M 80%	F 65%
Peak age of onset	21	30–50
Positive agglutination reactions	1%	50–70%
Nodules	0	10–20%
Persistent peripheral joints	25%	75–100%
Most common peripheral joints	Shoulders, hips, knees	Wrists, hands

from that seen in peripheral joint rheumatoid arthritis. Our opinion that the two diseases are distinct entities is based on several findings outlined in Table 2.

In Table 2, all percentages are approximate because each depends on the population sample obtained and the distribution curve of each finding is very broad. It is obvious that the sex incidence is quite different, spondylitis being a disease of young males and rheumatoid arthritis of women in their 30's and 40's. Positive serologic reactions and nodules are rarely seen in spondylitis. If one includes for the diagnosis of spondylitis all patients with a stiff painful back and x-ray evidence of sacroiliac changes, persistent peripheral joint involvement is not the rule. If peripheral joint involvement is present, however, root joints are most frequently affected. The micropathologic changes seen in rheumatoid arthritis, other than the nodule, are too nonspecific to warrant the conclusion of pathogenetic identity. The clinical features of joint involvement

supposedly pathognomonic of rheumatoid arthritis may be mimicked in other disease states—the shoulder-hand syndrome, nerve compression, and even multiple myeloma with para-amyloid. In sacroiliac x-rays of 50 patients with typical peripheral joint rheumatoid arthritis we found sacroiliac involvement in only two; in both, the disease started before puberty.

In peripheral joint rheumatoid arthritis, genetic forces have been weakly implicated. There is little doubt, however, that spondylitis is a genetically linked disease. It has been observed in identical twins. When a female has the disease, its appearance in male siblings is highly probable. Genetically, it is considered to be an autosomal dominant with 70% penetrance in the male and 10% penetrance in the female, with an over-all prevalence of 6 per 10,000 population (34).

Back involvement is the distinct clinical feature. It begins as stiffness after inactivity, then progresses to lumbar pain with root radiation, often sciatic in distribution. The back is held rigidly, with no separation of the lumbar posterior spinous processes on forward bending. Early, this is primarily due to muscular splinting, since it can be completely overcome by muscle relaxants such as curare or myanesin. Early in the disease, abnormal x-ray findings may be absent. Usually the first to appear is sacroiliac involvement. This must be distinguished from condensing iliitis in which only the ilial side of the joint is involved—considered by many to be a manifestation of a degenerative process. In spondylitis, the sacrum and ilium adjacent to the joint show increased radiodensity, occasionally punched-out areas, and, in some instances, ultimately bony fusion of the joint. The sacroiliacs are most readily seen in profile with a 35 or 45° angle posteroanterior view. The next x-ray phase is involvement of the diarthrodial joints of the spine appearing as condensation of bone and narrowing of the joint space. These joints are difficult to visualize with the best technique and require oblique films. The final phase is paravertebral ligamentous calcification. Frequently even early in the disease, vertebral demineralization, presumably on the basis of osteoporosis, becomes apparent. Costovertebral joint involvement, reflected clinically by decreased chest expansion, may be demonstrated roentgenographically by a complicated positioning technique requiring great skill in interpretation, but this is not necessary for routine patient care.

Peripheral joint involvement is frequently intermittent, lasting only a week or two and then subsiding. A few of our patients have had knee involvement of this kind a year before back symptoms have appeared. In about one fourth of our patients, peripheral joint involvement has been persistent, characteristically involving root joints (hence the synonym spondylitis rhizomélique). The x-ray changes in these joints are indistinguishable from those seen in peripheral joint rheumatoid arthritis. When persistent hip involvement is present with x-ray changes, the prognosis deteriorates.

A characteristic heart lesion has been described—aortic insufficiency. In our series of patients (we have no autopsies) are a few with the murmurs of aortic insufficiency and mitral stenosis indistinguishable from those of rheumatic heart disease. Iritis is more common with spondylitis than with peripheral joint rheumatoid arthritis but has no specific differentiating features.

The natural history in our patients follows a definite pattern. Pain is a major component in the first two or three years of disease. Spine stiffness and x-ray changes progress relentlessly but at a characteristic rate for each patient. The work record holds up quite well until the late 50's and 60's, when manifestations of senescence appear. Less than 10% of the patients are completely incapacitated.

One distinguishing feature of the patient with spondylitis is his effectiveness. Of our patients, 76% lead relatively normal lives in contrast to the 30–40% of our patients with peripheral joint rheumatoid arthritis who are significantly handicapped. In most rehabilitation studies, the spondylitic appears to be better motivated than what is taken as the equivalently affected peripheral joint rheumatoid arthritic. Whether this is a true difference, whether it is related to the kind of handicap imposed on each, or whether it has any causal significance are questions that have not been answered.

Management.—The principles of management are similar to those for peripheral joint rheumatoid arthritis. During the active phase, modification of the patient's life situation should be attempted and pain relieved to the best of one's ability. These patients usually can participate in regular activities without deterioration. Somewhat different approaches to the problem of pain relief are effective in this disorder. A special feature of preventing deformities is the maintenance of the back in the best functional position, which is the straight one.

For pain relief, aspirin remains the drug of choice. It should be used to the limit of tolerance and the opiates avoided. Radiotherapy has long been advocated to relieve the back pain of spondylitis. It is given through portals over painful areas of the spine, approximately 750 r in air per portal. The response may not be immediate, and a month or two should be allowed to elapse before treatment is considered a failure. All patients with spondylitis are not benefited by radiotherapy. Most workers feel that it is the treatment of choice, although several competent people disagree. The usual precautions against excessive spray radiation should be used, and treatment should not be repeated within two years. We have not seen late radiation effects, such as leukemia, in patients with whom these precautions have been observed, but leukemia following irradiation for spondylitis has been reported from Europe and Canada. The effect of radiotherapy is one of pain relief alone, and x-ray changes have been shown to advance in the absence of pain.

For unknown reasons, butazolidin seems to be quite effective in

many patients with spondylitis. This is particularly true of the patient with episodic attacks of pain usually induced by undue physical activity in these very active people. In these circumstances, a five-day course of butazolidin may abort an attack and decrease the possibility of sustained pain. In some instances, maintenance butazolidin dosage is required. Whenever this drug is used, certain precautions should be taken. Moderate sodium restriction is usually advisable; if not, weight should be recorded frequently to detect fluid accumulation. The development of agranulocytosis, thrombocytopenia, or incipient hemolytic anemia should be checked by weekly blood counts for the first two months of administration. Apparently, if bone marrow depression is going to develop, it will appear within that period. The other major complication of butazolidin administration is peptic ulceration, developing as long as 15 months after the start of treatment. A modified ambulatory ulcer regimen, consisting of frequent feedings and an aluminum hydroxide antacid in conjunction with butazolidin, has been suggested. Evaluation of this prophylactic program has only begun, and its value cannot at present be assessed. A severe bleeding ulcer is considered an indication for permanent withdrawal. There have been reports that agranulocytosis has not reappeared when the drug was begun again, but we have not been tempted to administer challenge doses in these patients. Butazolidin is slowly excreted—usually over five days—and its toxic effects persist during that period.

In a few instances—many fewer than with peripheral joint rheumatoid arthritis—when disease is sustained and when peripheral joint involvement is a major feature, steroid treatment should be considered. The indications and contraindications are identical with those described for peripheral joint rheumatoid arthritis. In our small series of patients in this category, the incidence of vertebral compression fractures has been greater than in patients with peripheral joint rheumatoid arthritis.

In prevention of deformities, principles similar to those outlined for the peripheral disease apply to peripheral joint involvement in spondylitis. In addition, the back—particularly the neck—should be kept in good functional position, and an attempt should be made to regain and maintain maximal chest expansion. These ends are accomplished by pain control, suitable rest positions, and active exercises. A flat bed, preferably with a board and a small pillow, minimizes neck flexion and kyphosis. Exercises are directed toward strengthening abdominal and paravertebral muscle groups and maintaining thoracic cage movement. One wishes to assure the patient a straight back and neck if complete fusion is the anticipated end-result. When forward flexion of the back has developed despite all efforts and life has become unbearable, a few hardy orthopedists have carried out osteotomies of the spine to correct the flexion deformity. This is a procedure of the most heroic pro-

portions, requires urgent indications, and, except in an extreme situation, should not be undertaken.

In spondylitis of the Marie-Strümpell type, with simple measures and a dedicated constancy of attention to detail, the end-result of a straight stiff but painless back is attainable in a large number of patients. In other words, for a chronic disease, spondylitis possesses certain attributes which permit the physician a moderate degree of optimism when looking into the future with his patient.

REFERENCES

Texts

Comroe's Arthritis and Allied Conditions, edited by J. L. Hollander (5th ed.; Philadelphia: Lea & Febiger, 1953).

Textbook of the Rheumatic Diseases, edited by W. S. C. Copeman (2d ed.; Baltimore: Williams & Wilkins Company, 1955).

Collins, D. H.: *The Pathology of Articular and Spinal Diseases* (Baltimore: Williams & Wilkins Company, 1950).

Primer on the rheumatic diseases, J.A.M.A. 152:323–331, 405–414, 522–531, 1953.

Journals

1. Bevans, M., *et al.*: The systemic lesions of malignant rheumatoid arthritis, Am. J. Med. 16:197, 1954.
2. Lamont-Havers, R. W.: Nature of serum factors causing agglutination of sensitized sheep cells and group A hemolytic streptococci, Proc. Soc. Exper. Biol. & Med. 88:35, 1955.
3. Heller, G., *et al.*: The hemagglutination test for rheumatoid arthritis: I. An immunological analysis of the factors involved in the reaction, J. Immunol. 69:27, 1952; II. The influence of human plasma fraction II (gamma globulin) on the reaction, ibid. 72:65, 1954.
4. Heller, G., *et al.*: IV. Characterization of the rheumatoid agglutinating factors by analysis of serum fractions prepared by ethanol fractionation, J. Immunol. 74:340, 1955.
5. Wager, O.: On the Factor Producing Agglutination of Sensitized Red Cells and Its Relation to the Agglutination of Hemolytic Streptococci in Rheumatoid Arthritis Sera (Dept. of Serology & Bacteriology, University of Helsinki, Finland, 1950).
6. Pike, R. M.; Sulkin, S. E., and Coggeshall, H. C.: The hemagglutination test for rheumatoid arthritis, M. Clin. North America 39:379, 1955.
7. Short, C. L., and Bauer, W.: Course of rheumatoid arthritis in patients receiving simple medical and orthopedic measures, New England J. Med. 238:142, 1948.
8. Reynolds, W. E., and Short, C. L.: The clinical manifestations of rheumatoid arthritis, M. Clin. North America 39:365, 1955.
9. Cobb, S.; Anderson, F., and Bauer, W.: Length of life and cause of death in rheumatoid arthritis, New England J. Med. 249:553, 1953.
10. Short, C. L., *et al.*: Rheumatoid arthritis with remission: A study of 80 patients, Ann. Rheumat. Dis. 13:362, 1954.
11. Ragan, C.: Rheumatoid arthritis: The natural history of the disease and its management, Bull. New York Acad. Med. 27:63, 1951.
12. Ropes, M. W., and Bauer, W.: *Synovial Fluid Changes in Joint Diseases* (Cambridge, Mass.: Harvard University Press, 1953).

13. Bunim, J. J., *et al.*: Rheumatoid arthritis: A review of recent advances in our knowledge concerning pathology, diagnosis and treatment, J. Chronic Dis. 1:168, 1955.
14. Sokoloff, L.: The heart in rheumatoid arthritis, Am. Heart J. 45:635, 1953.
15. Ebaugh, F. G., *et al.*: The anemia of rheumatoid arthritis, M. Clin. North America 39:489, 1955.
16. Hench, P. S., *et al.*: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions, Arch. Int. Med. 85:545, 1950.
17. Brown, H., *et al.*: 17-Hydroxy-corticosteroid metabolism in liver disease, J. Clin. Invest. 33:1524, 1954.
18. Fischer, F.: *Corticotropin and Cortisone in Rheumatoid Arthritis* (Copenhagen: Danish Science Press, 1955).
19. Bunim, J. J.; Ziff, M., and McEwen, C.: Evaluation of prolonged cortisone therapy in rheumatoid arthritis, Am. J. Med. 18:27, 1955.
20. Plotz, C. M.; Knowlton, A. I., and Ragan, C.: The natural history of Cushing's syndrome, Am. J. Med. 13:597, 1952.
21. Grokoest, A. W., and Demartini, F.: Systemic disease and the carpal tunnel syndrome, J.A.M.A. 155:635, 1954.
22. Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: Studies on metacortandralone and metacortandracin in rheumatoid arthritis, J.A.M.A. 157:311, 1955.
23. Bollet, A. J.; Black, R., and Bunim, J. J.: Major undesirable side-effects resulting from prednisolone and prednisone, J.A.M.A. 158: 459, 1955.
24. Hollander, J. L., *et al.*: Hydrocortisone and cortisone injected into arthritic joints, J.A.M.A. 147:1629, 1951.
25. Dawson, M. H.: A comparative study of subcutaneous nodules in rheumatic fever and rheumatoid arthritis, J. Exper. Med. 57:845, 1933.
26. Demartini, F.; Grokoest, A. W., and Ragan, C.: Pathological fractures in patients with rheumatoid arthritis treated with cortisone, J.A.M.A. 149:750, 1952.
27. Ragan, C., and Tyson, T. L.: Chrysotherapy in rheumatoid arthritis, Am. J. Med. 1:252, 1946.
28. Freyberg, R. H.; Block, W. D., and Levey, J.: Metabolism, toxicity and manner of action of gold compounds in the treatment of arthritis, J. Clin. Invest. 20:401, 1941.
29. Bertrand, J. J.; Waine, H., and Tobias, C. A.: Distribution of gold in the animal body in relation to arthritis, J. Lab. & Clin. Med. 33:1133, 1948.
30. Lowman, E. W.: Rehabilitation of the patient with chronic rheumatoid arthritis, J. Chronic Dis. 1:628, 1955.
31. Middlemiss, J. H.: Juvenile rheumatoid arthritis (Still's Disease), Proc. Roy. Soc. Med. 44:805, 1951.
32. Barkin, R. E.: Juvenile rheumatoid arthritis: A long-term follow-up, Ann. Rheumat. Dis. 11:316, 1952.
33. Coss, J. A., Jr., and Boots, R. H.: Juvenile rheumatoid arthritis: A study of 56 cases with notes on skeletal changes, J. Pediat. 29:143, 1946.
34. Stecher, R. M.: Hereditary factors in arthritis, M. Clin. North America 39:499, 1955.
35. Sokoloff, L., Wilens, S. L., and Bunim, J. J.: Arteritis of striated muscle in rheumatoid arthritis, Am. J. Path. 27:157-173, 1951.

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